REMARKS

Amendments To the Claims

With the present submission, claims 1, 15-18, 20, 32, and 36-39 have been amended. New claims 40-53 have been added. As such, claims 1, 15-18, 20, 32, and 36-53 are under consideration.

Claim 1 has been amended to recite "[a] chemically modified nucleic acid molecule, wherein: a) the nucleic acid molecule comprises a sense strand and a separate antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides; b) each strand of said nucleic acid molecule is independently 18 to 27 nucleotides in length; c) an 18 to 27 nucleotide sequence of the antisense strand of said nucleic acid molecule is complementary to HCV RNA sequence comprising SEQ ID NO: 1706; d) an 18 to 27 nucleotide sequence of the sense strand of the nucleic acid molecule is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of the HCV RNA sequence; e) about 50 to 100 percent of the nucleotides in the sense stand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications independently selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications; and f) one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2'-O-methyl purine nucleotides and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule are 2'-deoxy-2'-fluoro pyrimidine nucleotides." Support for amended claim 1 can be found in the as-filed application at, for example, page 7, lines 12-13; page 10, lines 4-6; page 11, lines 21-24; page 11, line 26, to page 12, line 12; page 13, lines 10-14; page 14, lines 12-19; page 15, lines 5-15; page 22, line 7, to page 23, line 10; page 26, lines 8-27; page 27, line 10, to page 30, line 9; Tables I, III & IV; and elsewhere. Support for amended claim 1 can also be found in the priority applications such as PCT/US03/05046, from which the instant application claims priority, for example, at page 6, lines 16-17; page 7, lines 7-9; page 8, lines 3-8, 23-28; page 19, line 26, to page 22, line 2; page 22, lines 15-25; page 45, lines 25-30; page 53, lines 2-6; page 62, lines 18-23; page 63, lines 1-5, 11-22; page 65, lines 1-3 (margin to Figure 19); page 124, line 29, to page 125, line 12; and elsewhere. Support for amended claim 1 can be further found in the priority

applications such as U.S. Provisional Application 60/363,124, for example, at page 4, lines 5-11; page 5, lines 14-17; page 10, line 3, to page 11, line 25; page 19, lines 11-14; page 20, lines 13-24; page 24, lines 15-22; page 29, lines 18 to 21; page 63, lines 19-31; Table (I); and elsewhere.

The term "siRNA" has been replaced by the term "nucleic acid" in each of claims 15-18, 20, 32, and 36-39, to insure proper antecedent basis. Moreover, the term "one or more" in each of claims 15, 18, and 36-39 has been replaced with by the term " 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more," in order to more particularly point out the number of the recited nucleotides in the designated strands. Further amendments have been made in claims 15-16, 18, 20, and 36-39 to correct unintended typographic errors, and/or to improve upon grammatical coherence of those claims without affecting their scope. Support for amended claims 15-18, 20, 32, and 36-39 can be found in the as-filed application as well as in the priority applications, such as PCT/US03/05043, and U.S. Provisional Application 60/363,124.

For example, support for amended claim 15 can be found in the as-filed application at, *inter alia,* page 14, line 29, to page 15, line 1; page 17, line 30, to page 18, line 2; page 18, lines 21-22; page 27, lines 22-27. Support for amended claim 15 can also be found in the priority applications such as PCT/US03/05046 at, *inter alia,* page 20, lines 6-11; page 64, lines 4-8. Support for amended claim 15 can be further found in the priority applications such as U.S. Provisional Application 60/363,124 at, *inter alia,* page 10, lines 1-30.

Support for amended claim 16 can be found in the as-filed application at, *inter alia,* page 15, lines 1-5; page 17, lines 20-27. Support for amended claim 16 can also be found in the priority applications such as PCT/US03/05046 at, *inter alia,* page 10, lines 23-26; page 19, line 26, to page 20, line 11. Support for amended claim 16 can be further found in the priority applications such as U.S. Provisional Application 60/363,124 at, *inter alia,* page 10, line 3, to page 11, line 25.

Support for amended claim 17 can be found in the as-filed application at, *inter alia,* page 17, lines 20-27. Support for amended claim 17 can also be found in the priority applications such as PCT/US03/05046 at, *inter alia,* page 10, lines 25-26; page 28, lines 11-13; page 29, lines 2-4. Support for amended claim 17 can be further found in the priority applications such as U.S.

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Provisional Application 60/363,124 at, *inter alia,* page 8, lines 21-25; page 13, line 18, to page 14, line 9; page 57, lines 8-13 (margin to Figure 9); Table (I).

Support for amended claim 18 can be found in the as-filed application at, *inter alia,* page 15, lines 7-10; page 17, line 32, to page 18, line 2; page 18, lines 21-22; page 27, lines 22-27. Support for amended claim 18 can also be found in the priority applications such as PCT/US03/05046 at, *inter alia,* page 20, lines 6-11; page 63, line 28, to page 64, line 3; page 64, lines 8-13. Support for amended claim 18 can be further found in the priority applications such as U.S. Provisional Application 60/363,124 at, *inter alia,* page 10, line 11, to page 11, line 25.

Support for amended claim 20 can be found in the as-filed application at, *inter alia,* page 26, lines 27-29. Support for amended claim 20 can also be found in the priority applications such as PCT/US03/05046 at, *inter alia,* page 19, lines 13-19. Support for amended claim 20 can be further found in the priority applications such as U.S. Provisional Application 60/363,124 at, *inter alia,* page 9, lines 23-28.

Support for amended claim 32 can be found in the as-filed application at, *inter alia,* page 20, lines 12-17. Support for amended claim 32 can also be found in the priority applications such as PCT/US03/05046 at, *inter alia,* page 42, line 28, to page 43, line 2. Support for amended claim 32 can be further found in the priority applications such as U.S. Provisional Application 60/363,124 at, *inter alia,* page 45, line 32, to page 46, line 13.

Support for amended claim 36 can be found in the as-filed application at, *inter alia,* page 27, lines 22-27. Support for amended claim 36 can also be found in the priority applications such as PCT/US03/05046 at, *inter alia,* page 10, lines 15-18; page 20, lines 6-11; original claim 11. Support for amended claim 36 can be further found in the priority applications such as U.S. Provisional Application 60/363,124 at, *inter alia,* page 10, lines 12-30; page 11, lines 1-25.

Support for amended claim 37 can be found in the as-filed application at, *inter alia,* page 14, line 29, to page 15, line 1; page 16, lines 29-32; page 72, lines 19-24. Support for amended claim 37 can also be found in the priority applications such as PCT/US03/05046 at, *inter alia,* page 63, lines 23-28. Support for amended claim 37 can be further found in the priority applications such as U.S. Provisional Application 60/363,124 at, *inter alia,* page 5, lines 14-17; page 10, lines 3-11, 17-25.

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Support for amended claim 38 can be found in the as-filed application at, *inter alia,* page 15, lines 5-10. Support for amended claim 38 can also be found in the priority applications such as PCT/US03/05046 at, *inter alia,* page 63, line 28, to page 64, line 3; page 64, lines 8-13. Support for amended claim 38 can be further found in the priority applications such as U.S. Provisional Application 60/363,124 at, *inter alia,* page 10, line 31, to page 11, line 25.

Support for amended claim 39 can be found in the as-filed application at, *inter alia,* page 19, lines 3-9. Support for amended claim 39 can also be found in the priority applications such as PCT/US03/05046 at, *inter alia,* page 11, lines 3-6; original claim 16. Support for amended claim 39 can be further found in the priority applications such as U.S. Provisional Application 60/363,124 at, *inter alia,* page 10, line 31, to page 11, line 25.

New claim 40 depends from claim 1, reciting "[t]he nucleic acid molecule of claim 1, wherein said nucleic acid molecule comprises one or more ribonucleotides." Support for new claim 40 can be found in the as-filed application at, for example, page 61, lines 28-29, and elsewhere. Support for new claim 40 can also be found in the priority applications such as PCT/US03/05046 at, for example, page 53, lines 17-18, and elsewhere. Support for new claim 40 can be further found in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 30, lines 17-19 (margin to Figure 10), and elsewhere.

New claim 41 also depends from claim 1, reciting "[t]he nucleic acid molecule of claim 1, wherein the 5'-end of said antisense strand includes a terminal phosphate group." Support for new claim 41 can be found in the as-filed application at, for example, page 19, line 30, to page 20, line 3, and elsewhere. Support for new claim 41 can also be found in the priority applications such as PCT/US03/05046 at, for example, page 18, lines 11-18, and elsewhere. Support for new claim 41 can be further found in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 8, line 26, to page 9, line 13, and elsewhere.

New claim 42 likewise depends from claim 1, reciting "[t]he nucleic acid molecule of claim 1, wherein 1, 2, or 3 of the purine nucleotides present in the sense strand are 2'-O-methyl purine nucleotides." Support for new claim 42 can be found in the as-filed application at, for example, page 27, lines 10-22; page 27, line 28, to page 27, line 7; and elsewhere. Support for new claim 42 can also be found in the priority applications such as PCT/US03/05046 at, for

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example, page 19, line 26, to page 20, line 6; page 130, Table I; and elsewhere. Support for new claim 42 can be further found in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 10, lines 3-11, 17-25, and elsewhere.

New claim 43 depends from claim 1, reciting "[t]he nucleic acid molecule of claim 1, wherein the antisense strand, sense strand, or both the antisense and sense strand include a 3'-overhang of 1-3 nucleotides." Support for new claim 43 can be found in the as-filed application at, for example, page 13, lines 1-7; page 15, line 16, to page 16, line 2; page 19, lines 18-26; and elsewhere. Support for new claim 43 can also be found in the priority applications such as PCT/US03/05046 at, for example, page 22, lines 15-25; page 28, lines 11-13; page 29, lines 3-6; and elsewhere. Support for new claim 43 can be further found in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 4, lines 9-11, and elsewhere.

New claim 44 depends from claim 43, reciting the nucleic acid molecule of claim 43 wherein the nucleotides of the 3'-overhang are chemically modified as specified. Support for new claim 44 can be found in the as-filed application at, for example, page 15, line 33, to page 16, line 2; page 19, lines 26-28; page 21, lines 21-25; page 26, lines 8-15; and elsewhere. Support for new claim 44 can also be found in the priority applications such as PCT/US03/05046 at, for example, page 28, lines 13-20; page 29, lines 14-16; and elsewhere. Support for new claim 44 can be further found in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, Table I, and elsewhere.

New claim 45 depends from claim 1, reciting the nucleic acid molecule of claim 1, further including "1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages" in one or both strands. Support for new claim 45 can be found in the as-filed application at, for example, page 22, line 7, to page 23, line 10; page 26, line 16, to page 27, line 9; and elsewhere. Support for new claim 45 can also be found in the priority applications such as PCT/US03/05046 at, for example, page 19, lines 3-13, 16-25, and elsewhere. Support for new claim 45 can be further found in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 9, lines 14-23, 28-30; page 11, lines 6-11; and elsewhere.

New claim 46 depends from claim 1, reciting the nucleic acid molecule of claim 1, further including "1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more 2'-O-methoxyethyl (MOE) nucleotides" in

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one or both strands. Support for new claim 46 can be found in the as-filed application at, for example, page 39, lines 2-11, 22-26; page 43, lines 25-29; and elsewhere. Support for new claim 46 can also be found in the priority applications such as PCT/US03/05046 at, for example, page 29, lines 20-32; page 30, lines 4-15; and elsewhere.

New claim 47 depends from claim 1, reciting the nucleic acid molecule of claim 1, further including "1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more locked nucleic acid (LNA) nucleotides" in one or both strands. Support for new claim 47 can be found in the as-filed application at, for example, page 35, lines 5-8, and elsewhere. Support for new claim 47 can also be found in the priority applications such as PCT/US03/05046 at, for example, page 26, lines 5-8, and elsewhere. Support for new claim 47 can be further found in priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 37, lines 28-31.

New claim 48 is independent, reciting "[a] chemically modified nucleic acid molecule comprising a sense strand and a separate antisense strand, wherein: a) each strand of said nucleic acid molecule is independently 18 to 27 nucleotides in length; b) an 18 to 27 nucleotide sequence of the antisense strand of said nucleic acid molecule is complementary to HCV RNA sequence comprising SEQ ID NO: 1706; c) an 18 to 27 nucleotide sequence of the sense strand of said nucleic acid molecule is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of the HCV RNA sequence; d) the sense strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends; e) one or more of the nucleotides present in the sense strand and one or more of the nucleotides present in the antisense strand are 2'-O-methyl modified nucleotides; and f) one to ten or more of the pyrimidine nucleotides present in the sense strand and one to ten or more of the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides." New claim 48 finds support in the as-filed application at, for example, page 7, lines 12-13; page 10, lines 4-6; page 11, lines 21-24; page 11, line 26, to page 12, line 12; page 13, lines 10-14; page 14, lines 12-19; page 15, lines 1-15; page 17, lines 20-27; page 22, line 7, to page 23, line 10; page 26, lines 8-27; page 27, line 10, to page 30, line 9; Tables I, III & IV; and elsewhere. New claim 48 also finds support in the priority applications such as PCT/US03/05046 at, for example, page 6, lines 16-17; page 7, lines 7-9; page 8, lines 3-8, 23-28; page 10, lines 23-26; page 19, line 26, to page 22, line 2; page 22, lines 15-25; page 45, lines 25-30; page 53, lines 2-6; page 62, lines 18-23; page

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63, lines 1-5, 11-22; page 65, lines 1-3 (margin to Figure 19); page 124, line 29, to page 125, line 12; and elsewhere. New claim 48 further finds support in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 4, lines 5-11; page 5, lines 14-17; page 10, line 3, to page 11, line 25; page 19, lines 11-14; page 20, lines 13-24; page 24, lines 15-22; page 29, lines 18 to 21; page 63, lines 19-31; Table (I); and elsewhere.

New claim 49 depends from claim 48, reciting a "composition comprising the nucleic acid molecule of claim 48 in a pharmaceutically acceptable carrier or diluent." New claim 49 finds support in the as-filed application at, for example, page 20, lines 12-17, and elsewhere. New claim 49 also finds support in the priority applications such as PCT/US03/05046 at, for example, page 42, line 28, to page 43, line 2, and elsewhere. New claim 49 further finds support in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 45, line 32, to page 46, line 13, and elsewhere.

New claim 50 is independent, reciting "[a] chemically modified nucleic acid molecule, wherein: a) the nucleic acid molecule comprises a sense strand and a separate antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides; b) each strand of the nucleic acid molecule is independently 18 to 27 nucleotides in length; c) an 18 to 27 nucleotide sequence of the antisense strand of the nucleic acid molecule is complementary to a HCV RNA sequence comprising SEQ ID NO: 1706; d) an 18 to 27 nucleotide sequence of the sense strand of the nucleic acid molecule is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of the HCV RNA sequence; e) at least 50% of the nucleotides of each strand of said nucleic acid molecule comprise modified nucleotides having a sugar modification selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, and deoxyabasic modifications; f) at least one of said sugar modifications is a 2'-O-methyl modification; and g) each strand of said nucleic acid molecule has no more than 3 consecutive ribonucleotides." New claim 50 finds support in the as-filed application at, for example, page 7, lines 12-13; page 10, lines 4-6; page 11, lines 21-24; page 11, line 26, to page 12, line 12; page 13, lines 10-14; page 14, lines 12-21; page 15, lines 5-15; page 16, lines 3-32; page 17, lines 5-19; page 20, lines 21-28; page 22, line 7, to page 23, line 10; page 26, lines 8-27; page 27, line 10, to page 30, line 9; Tables I, III & IV; and elsewhere. New claim 50 also finds support in the priority applications such as PCT/US03/05046 at, for example, page 6, lines

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16-17; page 7, lines 7-9; page 8, lines 3-8, 23-28; page 19, line 26, to page 22, line 2; page 22, lines 15-25; page 45, lines 25-30; page 53, lines 2-6; page 62, lines 18-23; page 63, lines 1-5, 11-22; page 65, lines 1-3 (margin to Figure 19); page 75, line 30, to page 76, line 2; page 124, line 29, to page 125, line 12; Table I; and elsewhere. New claim 50 further finds support in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 4, lines 5-11; page 5, lines 14-17; page 10, line 3, to page 11, line 25; page 19, lines 11-14; page 20, lines 13-24; page 24, lines 15-22; page 29, lines 18 to 21; page 42, lines 4-16; page 63, lines 19-31; Table (I); and elsewhere.

New claim 51 depends from claim 50, reciting a "composition comprising the nucleic acid molecule of claim 50 in a pharmaceutically acceptable carrier or diluent." New claim 51 finds support in the as-filed application at, for example, page 20, lines 12-17, and elsewhere. New claim 51 also finds support in the priority applications such as PCT/US03/05046 at, for example, page 42, line 28, to page 43, line 2, and elsewhere. New claim 51 further finds support in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 45, line 32, to page 46, line 13, and elsewhere.

New claim 52 recites "[a] method of modulating the expression of a HCV gene in a cell, comprising administering the chemically modified nucleic acid molecule of claim 1 to the cell under conditions suitable for modulating the expression of the HCV gene in the cell." New claim 52 finds support in the as-filed application at, for example, page 44, line 4, to page 45, line 8, and elsewhere. New claim 52 also finds support in the priority applications such as PCT/US03/05046 at, for example, page 35, line 16, to page 36, line 9, and elsewhere. New claim 52 further finds support in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 15, lines 10-26, and elsewhere.

New claim 53 recites "[a] method of modulating the expression of a HCV gene in a cell, comprising administering the chemically modified nucleic acid molecule of claim 50 to the cell under conditions suitable for modulating the expression of the HCV gene in the cell." New claim 53 finds support in the as-filed application at, for example, page 44, line 4, to page 45, line 8, and elsewhere. New claim 53 also finds support in the priority applications such as PCT/US03/05046 at, for example, page 35, line 16, to page 36, line 9, and elsewhere. New

claim 53 further finds support in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 15, lines 10-26, and elsewhere.

Amendments to the claims are made without prejudice or disclaimer, and do not constitute amendments to overcome any prior art or other statutory rejections. They are fully supported by the specification as filed, as explained above, and thus do not introduce new matter. Additionally, these amendments are not and should not be construed as admissions regarding the patentability of the claimed subject matter. Applicants reserve the right to pursue the subject matter of previously presented claims in this or in any other appropriate patent application. Accordingly, Applicants respectfully request the entry of the amendments presented herein.

Priority

The Office asserted that the effective filing date of the instant claims is determined to be that of application PCT/US03/05043, which has an effective filing date of February 20, 2003. *See* Office Action, at page 2. The Office declined to accord the instant claims the earlier, March 11, 2002, priority date, on which the priority U.S. Provisional Application 60/363,124 was filed. *See id.* Specifically, the Office alleged that "application '124 does not teach a limitation wherein 'about 100 percent of the nucleotide positions in one or both strands of the siRNA molecule are chemically modified' and 'the antisense strand of the siRNA molecule comprises about 5, 6, 7, 8, 9, 10 or more 2'-O-methyl nucleotides', as instantly recited in claim 1." Office Action, at page 3.

Applicants respectfully traverse and submit that the instant claims indeed find support in the '124 application, and therefore should be accorded the priority date of at least March 11, 2002, the date on which the '124 application was filed.

As discussed above in the "Amendments to the Claims" section, amended independent claim 1, as well as the newly added independent claims 48 and 50 all find support in the '124 application. Specifically, the claim element drawn to a chemically modified double stranded nucleic acid molecule finds support at, for example, page 3, lines 15-17; page 32, lines 11-12; page 35, lines 29-30; page 60, line 20; and elsewhere. The claim element drawn to the complementarity between the sense and antisense strands finds support at, for example, page 12, lines 4-7; page 19, lines 11-14; page 20, lines 16-20; page 21, lines 3-6; page 25, lines 17-29; and

elsewhere. The claim element drawn to antisense strand having 18 to 27 nucleotide complementary to the HCV RNA finds support at page 63, lines 19-31, and elsewhere.

Specifically addressing the Office's concerns, Applicants submit that the claim element drawn to "about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications ..." in amended claim 1e), and to "at least 50% of the nucleotides of each strand of said nucleic acid molecule comprises modified nucleotides having a sugar modification ..." in new claim 50e) are fully supported by the '124 application. For example, pages 10-11 of the '124 application teaches that the nucleic acid molecule having 1 to 10 phosphorothioate internucleotide linkages in both strands, one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro and/or universal base modified nucleotides, and a terminal cap moiety at the 3'-end, 5'-end, and/or both ends of either or both strands. The same section of the specification, and especially lines 6-11 of page 11, teaches that the nucleic acid molecule can, for example, have 1 to 10 phosphorothioate internucleotide linkages in either or both strands, 1 to 10 nucleotides of the nucleotides of the sense and/or antisense strands being chemically modified to comprise 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro and/or universal base modified nucleotides, and a terminal cap moiety at the 3'-end, the 5'-end, and/or both ends of either or both strands. As the claimed molecules are 18 to 27 nucleotides in length, those skilled in the art can readily deduce that about 50 to 100 percent of the nucleotides in the antisense and sense strands may be chemically modified in accordance with the '124 application.

Moreover, the '124 application provides numerous examples of chemically modified nucleic acid molecules having about 50 to 100 percent chemical modifications, especially at pages 55-57 of Table I, and in Figures 3-10. For instance, nucleic acid molecule 28254/28256 comprises about 50% chemical modifications on both strands. Other examples include, but are not limited to, 27653 and 27658 (both comprising 100% chemical modifications); 27655, 27654, 28254, 27662, 27659, 27660, 28244 (each comprising about 50 to 80 percent chemical modifications). Accordingly, U.S. Provisional Application 60/363,124 provides ample support for the claim elements described above.

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As extensively discussed in the "Amendments to the Claims" section of this response, the dependent claims also finds support in, *inter alia,* the '124 priority application. For the sake of brevity, Applicants do not reiterate the support for these claims here.

On the other hand, the Office appeared to take issue with the propriety of the priority claims to the '124 application. Office Action, at page 2. Specifically, the Office stated that "Applicants point to support in application 60/363,124 for some of the instant limitations. However the claims are essential subject matter. Essential subject matter may be incorporated by reference, but only by way of incorporation by reference to a U.S. patent or U.S. patent application publication, whereas application '124 is a provisional application." *Id.* (citing MPEP 608.01(p) and 37 CFR 1.57).

It is unclear how the limitations imposed on the incorporation by reference practice by MPEP 608.01(p) and 37 CFR 1.57 might, if at all, impact Applicants' right to claim priority to the '124 provisional application. Applicants respectfully note that in the same section of the MEPE, and especially under the subsection titled "Review of Application Which Are Relied on To Establish an Earlier Effective Filing Date," the MPEP unequivocally states that:

> [t]he limitations on the material which may be incorporated by reference in U.S. patent applications which are to issue as U.S. patents **do not apply** to applications relied on only to establish an earlier effective filing date under 35 U.S.C. 119 or 35 U.S.C. 120. Neither 35 U.S.C. 119(a) nor 35 U.S.C. 120 places any restrictions or limitations as to how the claimed invention must be disclosed in the earlier application to comply with 35 U.S.C. 112, first paragraph. Accordingly, an application is entitled to rely upon the filing date of an earlier application, even if the earlier application itself incorporates essential material by reference to another document. *See Ex parte Maziere*, 27 USPQ2d 1705, 1706-07 (Bd. Pat. App. & Inter. 1993).

(*emphasis added*). The same section of the MPEP further states:

> As a safeguard against the omission of a portion of a prior application for which priority is claimed under 35 U.S.C. 119(a)-(d) or (f), or for which benefit is claimed under 35 U.S.C. 119(e) or 120, applicant **may include a statement** at the time of filing of the later application incorporating by reference the prior application. … The inclusion of such

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> an incorporation by reference statement in the later-filed application will permit applicant to include subject matter from the prior application into the later-filed application without the subject matter being considered as new matter.

(*emphasis added*). Therefore, the priority claims made in the instant application are entirely proper, even including the express statement that "[t]hese [priority] applications are hereby incorporated by reference herein in their entireties, including the drawings," as recommended by the MPEP. *See* page 1 of the instant specification. Because the claims finds support in the '124 application, as explained above, they are entitled to the March 11, 2002, priority date, on which the '124 application was filed.

Rejections of Claims 1, 15-18, 20, 32, and 36-39 Under 35 U.S.C. § 103(a)

Claims 1, 15-18, 20, 32, and 36-39 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Wu *et al.* (Croatian Medical Journal, 42(4), 2001, pages 463-466), in view of Elbashir *et al.* (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), Pavco *et al.* (US 6,346,398 B1), Hammond *et al.* (Nature, 2001, Vol. 2, pages 110-119), Caplen (Expert Opin Bio Ther, 2003, Jul, (4), pp 575-586), and Parrish *et al.* (Molecular Cell, Vol. 6, pages 1077-1087, 2000). Applicants respectfully traverse.

a. Priority

Applicants respectfully note that the Office has accorded the instant claims the priority date of at least (or at the latest) February 20, 2003, on which the priority application PCT/US03/05043 was filed. Applicants further submit that, for reasons extensively discussed above and not repeated here, the instant claims are entitled to the March 11, 2002, priority date, on which U.S. Provisional Application 60/363,124 is filed. Therefore, at least one of the references listed above, namely, the Caplen reference, published in July of 2003, is not proper prior art to the present claims. Accordingly, the instant claims are not obvious.

Furthermore, the instant claims are not *prima facie* obvious in view of the legal standard of obviousness post-*KSR*, as explained below.

b. Post-KSR Legal Framework for Obviousness

Subsequent to the filing of Applicants' last response, the Supreme Court of the United States addressed the legal standards for determining obviousness under 35 U.S.C. § 103 in *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. 1727 (2007).

At the outset, reaffirming the objective standard for obviousness set forth in *Graham v. John Deere Co. of Kansas City* (383 U.S. 1, 17-18 (1966)), the *KSR* Court held that the teaching-suggestion-motivation test ("the TSM test") devised by the Federal Circuit Court of Appeals, if not applied in a rigid and mandatory fashion, is consistent with the *Graham* analysis. *KSR,* at 1731. Therefore, arguments and submissions regarding obviousness in Applicants' prior response, which does not follow the TSM test framework rigidly, are still valid post *KSR.*

The *KSR* decision focused on how to determine obviousness when all elements of a claimed invention can be found in the prior art. Recognizing that "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known," (*KSR*, at 1741), the Supreme Court emphasized three factors: (1) whether there is an "apparent reason to combine the known elements in the fashion claimed by the patent at issue," *id.* at 1740-41; (2) whether, when known elements are combined, there is predictability of yielding the claimed results; and (3) whether the prior art teaches away from modifying known elements in such a way that would lead to the claimed invention. The Court found obviousness in *KSR* because "there is a design need or market pressure to solve a problem [*i.e.,* a reason] and there are **a finite number** of **identified, predictable** solutions." *See id*, at 1732 (*emphasis added*). The *KSR* Court emphasized the importance of using teaching-away references to guard against hindsight reconstruction, stating that "[w]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *Id.* at 1740 (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)). As such, teaching away is significant not only in undermining the reason(s) for making a claimed invention, but also in diminishing the predictability of whether a combination of prior art elements may be successful. As discussed below, the prior art to the instant invention does just that, not only teaching away from making the claimed invention, but also suggesting the lack of predictability.

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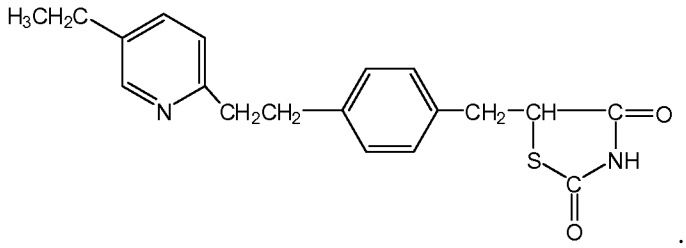
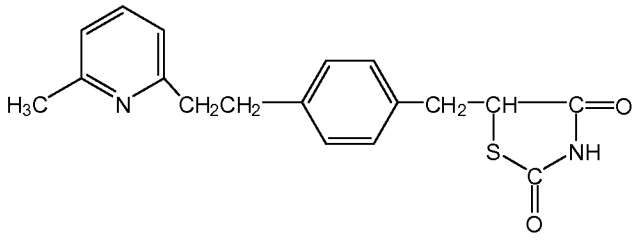
These factors have subsequently been interpreted by the Federal Circuit on several occasions. For example, applying the framework of *KSR,* the Federal Circuit held it necessary to demonstrate that the prior art provide reasons to make the particular invention and not merely general guidance before finding obviousness in *Pharmastem Therapeutics v. Viacell,* 83 U.S.P.Q.2d 1289, 1350 (Fed. Cir. 2007) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)), and stating that "an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it."). Therefore, the mere fact that certain approaches can be undertaken does not constitute a legally sufficient reason to combine the known elements in an obviousness inquiry.

Takeda Chemical Industries v. Alpharma, 2007 WL1839698, *15 (Fed. Cir. June 28, 2007), further illustrates the importance of having a finite number of identified, predictable solutions for a finding of obviousness. In *Takeda*, the claim at issue was directed to the compound pioglitazone, wherein an ethyl group is attached to the 5'-position of a pyridyl ring:



The alleged infringer argued that the claim at issue was obvious over the prior art compound b, which includes a pyridyl ring with a methyl group attached at the 6'-position:



The Federal Circuit agreed with the district court's finding of nonobviousness, despite the fact that the claimed compound differs from the alleged prior art compound in merely two aspects: (1) the type of substituent (methyl in compound b vs. ethyl in the claimed compound); and (2)

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the location of the substituent (at the 6-position on the pyridyl ring in compound b vs. at the 5-position in the claimed compound). The Federal Circuit found that the prior art would not have first led one of ordinary skill in the art to select compound b as a lead compound for investigation, and then led that person to make two obvious chemical changes: replacing a methyl group with an ethyl group, and "ring-walk" the ethyl group to the 5'-position, despite the fact that compound b was disclosed in a prior art reference. The Federal Circuit called attention to the fact that the reference disclosed hundreds of millions of other compounds in the same family, and exemplified 54 of those compounds, including compound b, but was silent as to which of those compounds would have the desired properties. The Federal Circuit also found it important that another reference also disclosed compound b, but did not identify it as one of the three most favorable compounds, and in fact singled it out as one having prominent undesirable side effects. On these facts, the Federal Circuit approved the district court's finding that a person of ordinary skill in the art would not have selected compound b as a lead compound.

The Federal Circuit then rejected the contention that, under *KSR*, it would have been obvious to pick compound b and modify it as claimed because the prior art compound fell within "the objective reach of the claim," and the evidence demonstrated that using the techniques of homologation and ring-walking would have been "obvious to try." According to the Federal Circuit, this was not a situation when there are a finite number of identified and predictable solutions to a problem. Instead, compound b "exhibited negative properties that would have directed one of ordinary skill in the art away from that compound." *Id.* at *15. Thus, the Federal Circuit concluded, "this case fails to present the type of situation contemplated by the [*KSR*] Court when it stated that an invention may be deemed obvious if it was 'obvious to try.'" *Id.*

The defendant's reliance on *Pfizer v. Apotex, Inc.,* 480 F.3d 1348 (Fed. Cir. 2007) fared no better. Contrasting *Pfizer*, where obviousness was found because the prior art teaches how to narrow the possibilities of a large family of lead compounds to a group of efficacious ones, the Federal Circuit pointed to the district court's finding of nothing in the prior art to narrow the possibilities of millions of lead compounds to compound b in *Takeda.*

The Federal Circuit went on to state that even if the prior art would have led to the selection of compound b as the lead compound, the obviousness argument failed on a second

ground. The Court found nothing in the prior art to suggest making the specific molecular modification to compound b that would lead to the claimed compounds. The Court also pointed out that studies have confirmed that several other compounds, "and one compound in particular, compound 99, that had no identified problems" in properties "differ significantly from compound b in structure." *Id.* at *18. The Court concluded that the process of modifying lead compounds was not routine at the time of the invention because of the great number of possible modifications, and because there was no way of predicting which of the modifications might bring about desired properties, especially in view of the fact that similar modifications did not always yield similar changes in properties. Therefore, there is no *prima facie* obviousness even when a general approach to a problem is known, if that general approach yields numerous choices, and the prior art does not help to predict which of those choices would be more efficacious.

Takeda also illustrates how a prior art reference teaching away from the claimed invention may further buttress the want of predictability. Specifically, evidence in the prior art that certain modifications produce undesirable properties should be taken as not only leading a skilled artisan away from those particular modifications, but also as suggesting the lack of predictability on how similar modifications may fare. In other words, if the prior art teaches that certain modifications sometimes but not always give rise to the desired properties, there is no way of predicting what other similar modifications may do.

c. The Cited References

Applying the post-*KSR* framework, Applicants submit that, at the time of the present invention, there was no reason for a skilled artisan to apply the chemical modifications of single stranded nucleic acid molecules to double stranded RNA molecules. In fact, at the time of the present invention, it was believed that dsRNA were substantially more stable than single stranded nucleic acid constructs, such as antisense and ribozyme oligonucleotides, and were therefore in need of little, if any, modification.

In this and previous Office Actions, the Office cited Caplen in support of the contention that those skilled in the art would have been motivated to apply chemical modifications known in the ribozyme and antisense art to siRNA duplexes. The Office quoted from Caplen that "[many

of the problem associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system," in support of that contention. Office Action, mailed August 1, 2006, at page 10 (quoting Caplen, at page 581). Applicants respectfully traverse.

First, contrary to the Examiner's contentions, the Caplen article does not establish that a person skilled in the art at the time of the present invention knew that RNA interference would encounter similar problems as other nucleic acid based therapies and would find motivation in incorporating the same types of modifications. As explained above, this article was published in July of 2003, **after** the earliest priority date of the present invention. Moreover, the statements quoted by the Examiner is found in the "Conclusion and expert opinion" section, which ostensibly illustrates the opinion or supposition of the author, who is an acknowledged expert (seeing that the article was published in the journal "Expert Opinion"), and is not indicative of what was known to a person of ordinary skill in the art at the time.

Second, Applicants respectfully submit that the Office has not satisfactorily explained why it would be within the purview of those ordinarily skilled in the art at the time of the present invention to find reasonable expectation of success. In direct contrast with Caplen, which does not inform on the level of knowledge possessed by those of ordinary skill in the art, the Elbashir article cited by the Examiner actually indicates the mindset of those skilled persons at the time, as evidenced by numerous research publications that came soon thereafter. Those publications uniformly suggested that skilled artisans followed the teachings of Elbashir, and designed siRNAs without any modifications other than the 2'-deoxythymidine nucleotides at the 3'-end of the siRNA. *See, e.g.,* Bitko *et al.*, 2001, BMC Microbiology, 1 (34), page 9, left column, "Materials and Methods;" Kuman *et al.,* 2002, Malarial Journal, 1(5), page 9, right column, "Transfection by Inhibitory dsRNA;" and Holen *et al.,* 2002, Nucleic Acid Research, 30, pages 1757-66, Figures 1, 2, and 6. Accordingly, those skilled persons were **in fact** led down a directly opposite path from the one taken by Applicants.

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Thus, the Office has failed to establish that there was a compelling reason to make modified dsRNA constructs, let alone the extensively modified constructs of the present claims.

More importantly, however, even assuming that a skilled artisan had found a reason to modify dsRNA constructs with the chemical modifications that were used with antisense or ribozyme (such as in Pavco) molecules, potentially hundreds of thousands, if not more, prospective chemical modification patterns may be generated in a double stranded nucleic acid molecule that is 18 to 27 nucleotides long. The cited references are either silent as to which of the modified molecules might be efficacious, or teach away from making certain of the modifications. Thus, the problem faced by Applicants at the time of this invention did not have a "finite number of identified, predictable solutions," and the instant claims are accordingly not *prima facie* obvious.

Countering Applicants' arguments that none of the cited references, alone or in combination, make obvious the presently claimed constructs, the Office alleged that "Elbashir et al. teach chemically modified siRNA molecules that retain siRNA activity when modified at 19% of the nucleotide positions and Parrish et al. teach extensively modified dsRNA molecules that retained RNAi activity." Office Action, at page 4. Moreover, the Examiner alleged that "Applicant's interpretation regarding the passage in the Elbashir et al. reference is considered erroneous," in that "Elbashir et al. teach … modification of 19% of the nucleotides with 2'-deoxy modifications with successful RNAi activity ...[, but] that 100% modification of one or both strands abolished activity. … Elbshir et al. is silent to any modification percentages between the successful example and the loss of activity at 100% and is silent to any other types of chemical modifications at any percentage." *Id.* at page 5.

Contrary to the Examiner's contentions, Elbashir is by no means silent as to the efficacy of chemical modifications between 19% and 100%. It specifically warns against using more than two 2'-deoxy modified nucleotides at the strands' 3'-ends or having any 2'-O-methyl modifications in "The siRNA user guide," which was cited in the prior response but reiterated here:

> 2'-deoxy substitution of the 2 nt 3' overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNAse resistance of siRNA duplexes. **More extensive 2'-deoxy or 2'-O-**

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methyl modifications, reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.

Elbashir (EMBO), at page 6885, left column *(emphasis added)*. Applicants note that the term "More extensive" in the second sentence could have only been intended to modify 2'-deoxy" and not the term "2-O-methyl," as the first sentence does not refer to "2-O-methyl" at all and the only experimental data involving 2´-OMe modified siRNA indicated that the corresponding constructs were inactive. Elbashir therefore teaches in no uncertain terms that 2'-O-methyl modifications should be entirely avoided.

Even if Elbashir could be taken as being silent with regard to the efficacy of chemical modifications between 19 and 100%, a contention to which Applicants strongly traverse above, Elbashir's silence does nothing to narrow the hundreds of thousands or more potential types, positions, and/or levels of chemical modifications that may take place in a double stranded nucleic acid molecule wherein each strand is 18 to 27 nucleotides in length. Indeed, as the Examiner has acknowledged, "regardless of the results of these specific modifications at 100% of the positions of one or both strands, Elbashir et al. did modify duplexes and published data regarding **successful inhibition with some duplexes and unsuccessful inhibitions with others**." Office Action, at page 5. Applicants respectfully submit that, rather than indicating the testing of known chemical modifications being routine, as the Examiner has concluded, the fact that some of the modified duplexes retain RNAi activity while others do not indicates that those highly skilled in the art, such as the authors of the Elbashir reference, could not predict what specific position(s), levels, or types of chemical modifications amongst hundreds of thousands or more of potential modification patterns would lead to a "successful" RNA duplex.

None of the other cited references serves to narrow down this choice. Not unlike the circumstances of *Takeda*, because of the great number of possible modifications patterns on a 18 to 27 nucleotide duplex, and because there was no way of predicting which of the modifications might bring about a molecule with RNAi activity, especially in view of the fact that similar modifications did not always yield similar changes in properties, the cited references do not render the instant claims obvious.

Accordingly, Applicants respectfully request the withdrawal of this rejection.

Claims 1, 15-18, 20, 32, and 36-39 stand rejected under 35 USC § 103(a) as being allegedly obvious over McCaffrey *et al.* (Nature, Vol. 418, July 2002, pages 38-39), in view of Elbashir *et al.* (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), Pavco *et al.* (U.S. 6,346,398 B1), Caplen (Expert Opinion Biol Ther, 2003 Jul, 3(4), pages 576-586), and Parrish *et al.* (Molecular Cell, Vol. 6, pages 1077-1087, 2000). Applicants respectfully traverse the rejection and apply the arguments above with equal force.

In sum, the instant claims are not obvious in view of the cited reference for the following reasons:

a. Caplen was published after the priority date of the instant application and thus is not proper prior art. Also, Caplen only indicated opinion(s) of an expert, not reflecting what those of ordinary skill in the art believed at the time of the present invention.

b. McCaffrey was published after the priority date of the instant application and thus is not proper prior art.

c. Those of ordinary skill in the art believed there was little or no need to modify double stranded nucleic acid molecules at the time of the present invention. Extensive evidence suggests that the skilled artisans were in fact led down a directly opposite path by the Elbashir reference from the one taken by Applicants.

d. Even if a reason could be found to modify double stranded dsRNA constructs with the chemical modifications that were used with antisense and ribozymes (such as in Pavco) molecules, potentially hundreds of thousands or more prospective chemical modification patterns may be generated in a double stranded nucleic acid molecule that is 18 to 27 nucleotides long in each strand. None of the cited references teaches how to narrow down this large number of choices to those that are active.

e. The fact that "Elbashir did modify duplexes and published data regarding successful inhibition with some duplexes and unsuccessful inhibitions with others," as recognized by the Office, is further evidence that those skilled in the art had no way

of predicting which among the hundreds of thousands, if not more, potential modification patterns would lead to active siRNA duplexes.

Accordingly, the instant claims are not rendered obvious by McCaffrey *et al.* (Nature, Vol. 418, July 2002, pages 38-39), in view of Elbashir *et al.* (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), Pavco *et al.* (U.S. 6,346,398 B1), Caplen (Expert Opinion Biol Ther, 2003 Jul, 3(4), pages 576-586), and Parrish *et al.* (Molecular Cell, Vol. 6, pages 1077-1087, 2000). Applicants thus respectfully request the withdrawal of this obviousness rejection.

Conclusion

In view of the foregoing remarks, Applicants submit that the claims are in condition for allowance, which is respectfully solicited. If the Examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

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